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SUBLINGUAL MISOPROSTOL: A RATIONAL CHOICE FOR TREATING FIRST TRIMESTER MISSED MISCARRIAGE IN OUTPATIENT SETTINGS

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ABSTRACT

Objective: To evaluate the role of sublingual misoprostol in first trimester missed miscarriage among women seeking medical management as outpatient.

Methodology: A descriptive cross sectional study was conducted at Hayatabad Medical Complex, Gynecology department, involving 179 women recruited through consecutive sampling. Eligible participants were women of reproductive age(20-40years) with singleton first-trimester miscarriage (<13 weeks gestation), residing near the hospital(at 15-30min distance) having >10Hb, hemodynamically stable and no active ongoing blood loss. The selected women received a single dose of 600 µg sublingual misoprostol in crushed form and were followed up for clinical and sonographic assessment of complete expulsion of conceptus.Data entry and analysis were performed using SPSS version 22.

Results: Out of 179 women, 119 expelled the conceptus completely. Remaining patients switched over to other options due to retained products of conception or heavy bleeding.Success rate of sublingual misoprostol was found to be 66.5% .Satisfaction and acceptability is high for medical management of miscarriage 76.67% and 68.33% respectively,with statistically significant difference for satisfaction (p-0.004).

Conclusion: Sublingual misoprostol is found to be effective in first trimester missed miscarriage among women seeking medical management as out patient.

Keywords: Missed Miscarriage; Misoprostol; Medical Management; Surgical Management.

INTRODUCTION

Pregnancy is a dynamic process with varying outcomes in women's life. Fetal viability at a point does not imply that pregnancy will continue till plausible outcome. Failure of pregnancy pulls the woman towards low self esteem and she needs psychological support in such situation.¹ A successful pregnancy is dependent on the integration of complex hormonal, immunological, genetic and cellular cascade which involves an organized series of events ensuing from conception, implantation and ending upon the development of fetus.²

Loss of pregnancy during first 24 weeks of gestation is termed as miscarriage where as World Health Organization defines the miscarriage as pregnancy loss before 20 weeks of gestation or loss of fetus weighing 500 grams or less.³ An early Missed miscarriage is a common form of miscarriage, where ultrasound shows no growth of intrauterine sac/embryo and/or loss of fetal heart activity before 14 weeks of gestation. It is also

called silent or delayed miscarriage.⁴ Most common complication of the human pregnancy is early miscarriage, occurring during first trimester. Early pregnancy loss affects 10 to 20% of clinically diagnosed pregnancy. 80% of miscarriage occur before 13 weeks of gestation, out of which 75% cases does not proceed beyond 8 weeks of gestation .Approximately 32% of implanted conceptus spontaneously abort near the onset of next expected menstrual cycles and remains unrecognized and termed as sub clinical miscarriage after clinical recognition of pregnancy.⁵

Management of first trimester can be done in one of the following three ways i.e expectant, medical or surgical modality depending on women's condition and desires. First line treatment is expectant treatment with 85% success rate, if it fails then medical treatment is preferred. Medical treatment is successful in 90%of cases with only 10% failure, requesting for other methods of miscarriage.^{6,7}

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Misoprostol, a prostaglandin E1 analogue has attracted the attention over past few decades in various regimens for missed miscarriage. It was initially introduced as a gastric ulcers protective agent in 1970s, later on recognized for its amazing effects on cervical ripening and myometrial contractions which made it a drug of choice for the medical treatment of missed miscarriage and induction of labour. As compared to the surgical method of miscarriage medical method utilizing misoprostol has an additional advantage of decreased cervical injuries, minimal blood loss and reduced requirement for general anesthesia.⁸

A pharmacokinetics study suggests that sublingual is the most potent route for misoprostol due to its highest bioavailability and shortest time to reach peak concentration, which may be due to the absence of first pass effect by liver, good blood supply under tongue and the neutral pH of buccal cavity.⁹

International organization like WHO, FIGO, and NICE have approved Misoprostol for management of miscarriage. Misoprostol is a synthetic analogue of naturally occurring Prostaglandin E1. It is a cheap, heat stable drug that doesn't require cold chain maintenance. Different routes of administration include oral, sublingual, vaginal or rectal route with appropriate dosage protocols to avoid complications.¹⁰ There is a wide variation in the reported success rate of medical management of miscarriage, between 13% and 90%.¹¹

Ambulatory gynecology avoids the cost and morbidity of hospital admission, providing safe acceptable and convenient treatment to women. Immense body of literature is available on medical management of miscarriage, nevertheless the ideal route and regimen needs to be evaluated among women having first trimester miscarriage as an outpatient management option. Successful medical management in outpatient

department might contribute to the reduction strategies of healthcare expenses in developing countries as well as burden on hospital resources. So the aim & objective of our study is to evaluate the role of sublingual misoprostol in first trimester missed miscarriage among women seeking medical management as outpatient.

METHODOLOGY

It was a descriptive cross sectional study conducted at Hyderabad medical complex from 1st January 2022 to 1st December 2022. Approval of the study was acquired from institutional research and ethical board (Ref: IERB/HMC/1184/14-2-2023). Sample Size was calculated by WHO sample size software. Taking 35% risk of Dilatation and Curettage, margin of error 7% and 95% confidence interval, the sample size was 17912.

A total of 179 women were recruited as per selection criteria. Sample collection was done by non probability consecutive technique. All woman of reproductive age (20-40years), living in the outskirts of hospital (15-30 min distant) with history of having singleton pregnancy diagnosed with missed miscarriage at or before 13weeks of gestation and seeking medical management for miscarriage, Hemoglobin > 10gm/dl, hemodynamically stable with no active ongoing blood loss were included in this study.

All Women who opted for alternative method of management of miscarriage, had history of incomplete miscarriage, life-threatening hemorrhage, history of organic lesion in uterus (Fibroid, Mullerian anomalies etc), contraindications to misoprostol, had a history of bleeding disorders or using anticoagulants and woman with history of prior failed surgical or medical attempts of miscarriage during the current pregnancy and woman belonging to far flung areas were excluded from this study.

Patients were counseled that they may need surgical evacuation in case of failed medical treatment of miscarriage or torrential vaginal bleeding not letting her to wait until the effects prevail. Miscarriage was declared on clinical assessment of the uterine size in relation to period of gestation and ultrasound evidence. Departmental ultrasound was done with instant second opinion from on duty senior sonologist there and then.

Diagnosis was made according to RCOG guidelines, new ultrasound criteria for the diagnosis of miscarriage on initial scan include an empty gestational sac of MSD at or beyond 25 mm or an embryo with CRL at or beyond 7 mm and no heartbeat .

These findings should be confirmed with the second opinion or repeat scan performed 7 days after the initial scan. Patients were explained about the procedure and detailed informed consent was taken before hand. All woman included in this study were completely evaluated. Their detailed history, clinical and ultrasound examination was performed. Blood sample was collected for Full blood count, clotting profile, blood group with Rh factor. Immunoglobulin was administered to rhesus negative subjects where indicated. All the information including recruitment date, age, gravidity, parity, LMP, date of treatment, duration of bleeding, amount of blood loss (in relation to regular menstrual flow) and side effects if any were recorded on pre designed proforma.

Termination of pregnancy was done by offering sublingual misoprostol. Since women were managed as outpatient case, their distance from hospital was 15 to 30 minute and contact numbers were shared in case of any emergency to prevent any serious complication. Women belonging to far flung areas were not offered this regimen in view of they might not be able to reach hospital due to far off location so we included the local participants in this study to avoid any incon-

venience and unforeseen event of hemorrhage and its consequences.

All eligible candidates were counseled and provided with detailed information about the protocol, consenting women were advised to have 600 ug sublingual misoprostol in crushed form and stay for next 4 hours in hospital. Patients were informed about the side effects (shivering/chills, diarrhea, abdominal pain, hyperthermia, nausea, vomiting, flatulence, constipation, dyspepsia, headache) and their resolution. Follow up after 3 days with instruction of emergency visit to hospital in case of heavy bleeding or may contact in case of any worrisome or additional concerns. Patient was followed till the completion of expulsion/evacuation. On day-3 follow up visit pelvic ultrasound was advised. Ultrasound with no RPOCs was declared as successful medical management of miscarriage. In case of endometrial thickness >15 mm but no clinical symptoms she was advised for second follow up on day 10 for pelvic ultrasound. In case of failed medical treatment, heavy bleeding (>menstrual blood flow for >3hours) or blood loss affecting vital signs and women who didn't wish to wait for second follow up visit, most of them opted for surgical methods either manual vacuum aspiration or conventional evacuation and curettage. Rest of women took the second cycle of same regimen and responded.

All of these issues, side effects and potential risks of treatment were addressed explicitly by proper counseling and education of patients beforehand. They were asked to maintain a diary for recording days of bleeding and occurrence of side effects. A few operational definitions are as follows:

Ultrasound confirmation of no intrauterine remnants and bleeding not exceeding normal menstrual flow was considered successful management. Patient with failed treatment or incomplete miscarriage opted for other

methods i.e: repeat cycle, expectant management or surgical method of miscarriage.

Acceptability by patient was measured in terms of the same choice in future, if required and recommendations to others seeking medical treatment. Patient satisfaction with the procedure was assessed through self-evaluation during the final follow-up. The reasons for dissatisfaction were documented, including issues such as excessive bleeding, anxiety, intolerance of side effects, and prolonged follow-up.

The primary objective of the study mainly focused on the complete expulsion of the intervention without resorting to surgical evacuation for any cause. Additional outcome measures encompassed adverse effects, pain levels, acceptability, and overall satisfaction. Given the study's objective to evaluate women's contentment and acceptability of the method, participants were specifically asked whether they would opt for the method again if given the choice. Data entry and analysis utilized SPSS 22, calculating frequencies, means, standard deviations, and percentages for variables such as age group, gravidity, parity, history of previous cesarean section, success rate, satisfaction, and patient acceptability. The Chi-square test was employed to compare outcome measures, with a p-value of 0.05 deemed statistically significant.

RESULTS

Total of 179 women diagnosed with missed miscarriage who fulfilled the inclusion criteria were offered medical treatment. 600µg misoprostol through sublingual route administered. Total 119 women expelled the conceptus completely within 24 hours to 7 days period. Rest of the patients switched over to other options due to heavy bleeding, incomplete miscarriage and failed treatment. The baseline characteristic of the participants in each group are presented and com-

pared in table 1.

Mean age of the participant was 29.66 years; mean gravidity was computed as 2.8 and parity 1.8. Mean period of gestation was calculated as 10 weeks. Table 2 shows further details of demographic data in terms of age, gravidity, parity, gestational age. Table 3 shows the effectiveness and success rate of medical treatment. Table 4 showing the acceptability and satisfaction, both were found high in medical group. Whereas figure 1 shows the different reasons of switching over to other options for termination of pregnancy.

DISCUSSION

In this study we tried to evaluate the role of sublingual misoprostol in first trimester missed miscarriage among women seeking medical management as outpatient, keeping in view that ambulatory gynecology avoids the cost and morbidity of hospital admission, providing safe, acceptable and convenient treatment to women.

Our result demonstrates a success rate of 66.5% for patients managed with sublingual misoprostol as outpatient case. This success rate was higher but not significant statistically (p=0.713). Our findings corroborate the results of Afanet al¹³ and Ehsan et al¹⁴ who reported 76.6% and 72% success rate respectively. Hence in their research study efficacy of sublingual misoprostol was not only higher than other methods of same study, but these results surpasses the success rate reported by our research study as well.

Our study depicted that mean age of women in study group was 29.66 + 5.361 years but the difference between the groups was not significant statistically (p = 0.713). Majority of women were multiparous in both the groups. Our findings were consistent with the study conducted by Elsalem SA et al¹⁵

Table 1: Descriptive Statistics of Study n= 179

Numerical Variable	Minimum	Maximum	Mean	Standard Deviation
Age (years)	20	40	29.66	5.361
Gravidity	3	6	2.80	0.750
Parity	2	5	1.80	0.750
Gestational Age (Weeks)	8	12	10	1.676

Table 2: Demographic Data and Obstetric Characteristics n= 179

Variables Characteristics	Medical Treatment (Misoprostol)		Total	P-Value
	Complete Expulsion	Need of other Treatment/ Method		
Age 20-30 Years	62 (52.1 %)	30 (50 %)	92 (51.4 %)	0.713
31-40 Years	57 (47.9 %)	30 (50 %)	87 (48.6 %)	
Total	119	60	179	
Gravidity < 4	104 (87.4 %)	51 (85 %)	155 (86.6%)	0.342
>4	15 (12.6 %)	9 (15 %)	24 (13.4 %)	
Total	119	60	179	
Parity < 3	104 (87.4 %)	51 (85 %)	155 (86.6%)	0.342
> 3	15 (12.6 %)	9 (15 %)	24 (13.4 %)	
Total	119	60	179	
POG >9 weeks	95 (79.83 %)	14 (23.33 %)	109 (60.9 %)	0.532
> 3	24 (20.17 %)	46 (76.66 %)	70 (39.1 %)	
Total	119	60	179	

Table 3: Effectiveness of Medical Treatment n= 179

	Complete Expulsion	Frequency	Percentage	P-Value
Misoprostol Administration	Yes	119	66.5 %	0.713
	No	60	33.5 %	
	Total	179	100 %	

Table 4: Satisfaction and Acceptability of Patients n: 179

Variables		Misoprostol GP n = 119	Other Method GP n = 60	P-Value
Satisfaction	Yes	117 (98.3%)	46 (76.67 %)	0.004
	No	02 (1.7 %)	14 (23.33%)	
	Total	119	60	
Acceptability	Yes	111 (93.3%)	41 (68.33%)	0.183
	No	08 (6.7%)	19 (31.66%)	
	Total	119	60	

who reported that 69.7% of patients were above 30 years. In contrast to our findings Naila et al¹⁶ showed 34.6 years as mean age of women consented to use sublingual misoprostol as medical management option.

In 2012, the International Federation of Obstetrics and Gynecology formulated a chart outlining the suggested dosages of misoprostol for diverse obstetrical and gy-

necological purposes. This chart was subsequently revised and updated in 2017 by a team of experts. While the recommended dosages were established based on existing evidence and expert opinions, it is essential to acknowledge that new evidence continually surfaces. Consequently, there is an ongoing requirement to periodically review and modify these recommendations in the future.¹⁷

The results of this study have demonstrated that the use of single dose of 600µg sublingual dose of misoprostol is a cost effective and acceptable method of medical treatment of first trimester miscarriage. On the contrary, surgical management of miscarriage incurs much more costs than medical management of miscarriage on average after initial treatment. The high efficacy of 600µg sublingual misoprostol is similar to

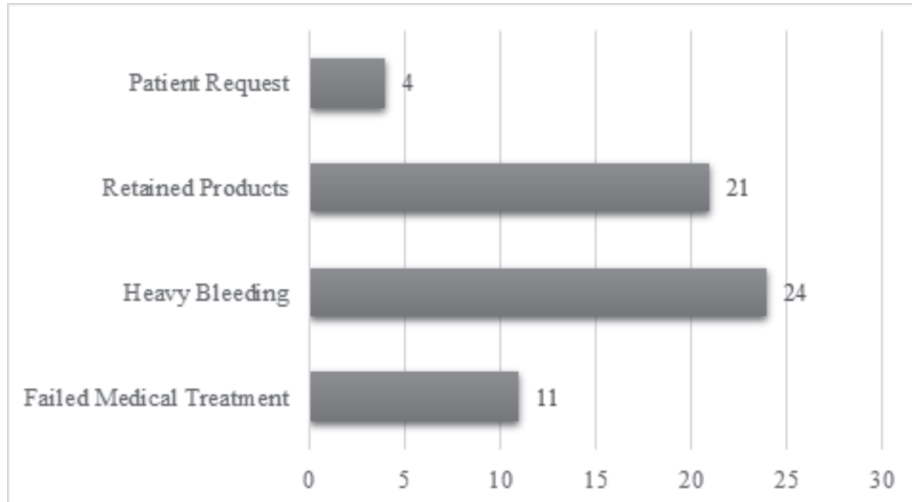


Figure 1: Reason for Switch over to other options n=60

that shown by Saeed S et al¹⁸ 200 µg oral misoprostol for hourly, maximum of 4 doses. Latif S et al¹⁹ tried 600 µg sublingual misoprostol and in case of failure further 400 microgram was repeated for maximum of two doses and the success rate was 73.3%. It is observed that increasing the dose and shortening the interval of misoprostol does not improve the complete miscarriage rate. Regimen using single or repeated dose of misoprostol alone completing in one day have the advantage of requiring less hospital visits and usage of health resources.^{18,19} By changing the route of administration from conventional to sublingual, a complete miscarriage rate of 66.5% was achieved in our study with no serious complications or adverse effects. However more studies are required to confirm the safety of the sublingual misoprostol protocol.

Our study revealed that women in medical management group admired the method's simplicity and also satisfied with the medical method. The satisfaction rate was statistically significant ($p=0.004$) where as acceptability was higher but the difference between the two groups was not significant statistically ($p=0.183$).

Hence the data showed that women in the misoprostol group were significantly

satisfied with their treatment. When asked about future selection of either method (acceptability), it was again noticed as higher in medical group but the difference was not significant statistically.

Sharma et al found higher efficacy in women who had sublingual misoprostol for miscarriage. According to them the side effects of medical management of miscarriage were bothersome as compared to surgical method of miscarriage.²⁰

Despite the fact that surgical method of miscarriage is considered extremely effective but it possesses variable risk of anesthesia and/or surgical complications.²¹ Women declining the surgical Management due to potential risks may find the misoprostol as a suitable choice for medical treatment of first trimester miscarriage.²² Sublingual route offers more comfortable dose, greater privacy and easily controllable adverse effects.²³

Easy availability, cost effectiveness, convenient dosage, minimum side effects profile, patient's acceptability and satisfaction make the sublingual misoprostol a method and drug of choice for medical management of miscarriage. Medical method of miscarriage decreases the surgical burden and inpatient workload on health care services and

avoids the complications associated with surgical methods of miscarriage.

LIMITATIONS

Our study had the strength of prospective study which can minimize the risk of recall and information bias. Moreover an immense body of literature is available on this subject however a limited local data is available as outpatient management. This study is a struggle towards outpatient management protocols. Nevertheless the study has some limitations affecting the generalization of results since it is a single centered study with relatively small sample size. Therefore, a multicentric study is required.

CONCLUSIONS

The rate of successful miscarriage was 66.5% in medical Management group of our study. Medical management of miscarriage via misoprostol is a rational and prudent outpatient choice among women diagnosed with first trimester missed miscarriage. The substantial reduction of burden on Gynae Unit managing first trimester complications as observed in this study advocates its promising potential as a novel medical treatment. Therefore, our study indicates that misoprostol through sublingual route could be a valuable addition to the current arsenal of medical management, especially for patients reluctant to surgical or medical-treatment as in patient.

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Author's Contribution

NK conceived the idea, performed data analysis, helped in the write up of the manuscript. S, SM and LA designed the study and collected the data. RK performed data analysis, designed the study and collected the data, and performed data analysis. All authors made substantial intellectual contributions to the study.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.